United States Court of Appeals

for the

District of Columbia Circuit

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IN THE

Court of Appeals, District of Columbia

JANUARY TERM.

No. 2257. 802

THE UNITED STATES OF AMERICA, *Appellant*,

vs.

THE ANTIKAMNIA CHEMICAL COMPANY, *Appellee*.

ADDITIONAL BRIEF FOR APPELLEE FILED BY LEAVE OF COURT.

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PRESS OF BYRON S. ADAMS, WASHINGTON, D. C.

UNITED STATES OF AMERICA

vs.

ANTIKAMNIA CHEMICAL COMPANY.

CONTENTS OF APPELLEE'S ADDITIONAL BRIEF.

FIRST PART:

(a) Brief of Additional Argument;

(b) Replies to contentions of United States District Attorney, and of appellant's supplemental brief;

(c) Authorities on the question of judicial notice of chemical properties and therapeutical and physiological effects of drugs involved herein.

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I.

Extracts from Pharmacopœia of the United States of America, defining:

(a) Acetanilide;
(b) Acetphenetidin.

II.

Extract from the United States Dispensatory, giving USES and effects of:

(a) Acetanilide;
(b) Acetphenetidin.

III.

Extract from report of Senate Committee on Manufactures, 58th Congress, 2d Session, January 15, 1904, accompanying Senate Bill 198, relating to "Adulteration of Foods, etc.," and containing statements of Dr. Wiley, of Department of Agriculture, relative to phenacetine (Acetphenetidin) and Acetanilide.

IV.

Extract from hearing before Senate Committee, January 20, 1903, of hearings on H. R. 3109, being the Pure Food and Drugs Act, containing statements relative to the use of Acetanilide as an adulteration of or substitution for Acetphenetidin (Phenacetine).

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Since the filing of our brief, the appellant filed a supplemental brief, apparently prepared by the Agricultural Department. For this reason and on account of the position of the appellant in the argument, the following is submitted:

We reiterate that there is nothing in the Act that requires the adding to the label where the word "Acetphenetidin" is placed thereon the words "a derivative of acetanilid." To maintain its position on this point, the appellant claims: (1) that the Act itself requires it; and (2) that the regulation requires it, and that the regulation is lawful and valid, in that it was within the power of the several secretaries to make the same. We have so fully considered these contentions in our original brief that it might be repetition to again call the Court's attention thereto.

The first proposition of the appellant that the Act itself requires it, is repudiated by the wording of the Act. Let us read the Act, eliminating everything of surplusage; "or if the package fail to bear a statement on the label of the quantity or proportion of * * * acetanilid or any derivative or preparation of any such substances contained therein." Now read the Act in this way: "or if the package fail to bear a statement on the label of the quantity or proportion of any * * * acetanilid or any derivative or preparation of acetanilid." Is not this what the Act means? And, if that is so, how can the contention of the Government be sustained?

To sustain his contention, the United States Attorney says that these drugs are habit-forming drugs; of this fact we have no evidence.

He says further that acetanilid and acetphenetidin are chemically alike, something with which we have nothing whatever to do.

He says further that they produce the same physiological effect; something that the libel does not say.

For these reasons he says that where we use the word "acetphenetidin," we must add thereto that it is a derivative of acetanilid. When questioned by the Court as to whether every derivative when named would have to be followed by the name of the parent substance, the District Attorney said, *if the derivative does not follow in effect the parent, then no law would be violated if you fail to state the name of the parent.* Thus under his own construction of the Act, he would require every individual to be not only a chemist, but also to be an expert in therapeutics and physiology; to determine whether or not on a label such person had to add after the name of a derivative the name of its parent. The answer of the United States Attorney to the question propounded by the Court shows the fallacy of the contention of the appellant. In one case where a label naming a derivative failed to state the parent, a punishment could not be imposed, and in another a punishment could be imposed. Such argument falls of itself.

None of the cases referred to in the supplemental brief, or in the original brief, filed by the appellant, sustains its position that under the law this prosecution could be maintained without regard to the regulation. The appellant relies upon *In re Kollock,* 165 U. S., 532. In that case, as said by this Court in the case of *United States vs. Prather,* the statute defined the offense in the body of the section making the act of the manufacturer or retailer penal, reference was made to everything necessary to make up the offense and, therefore, reading the statute, the Court said you could read the crime. Reading this statute from the Government's own position, one is unable to tell what is or what is not a violation of the law.

The second proposition of the Government is that the regulation requires the naming of the parent substance, as well as the derivative, and that the regulation is lawful and valid, being within the power of the several secretaries.

Under this contention, as well as under the second proposition put forward in our brief, it is immaterial whether the statute is a penal or a remedial one; for, if the regulation adds to, alters or amends, the statute, or imposes a penalty for an act not imposed by the statute, then, even if the statute is remedial, the regulation is null and void. Chief Justice Clabaugh, in deciding this case in favor of the appellee, held that it was not necessary for him to determine whether or not the statute was a penal statute, saying that the regulation was, in his opinion, an addition to the Act and, therefore, whether the Act was penal or remedial, the Secretaries had no power or authority to make it.

In arguing this second proposition, the Government took the broad ground that this regulation was valid and that a person could be punished by the seizure of his goods for violating the regulation, although there was no provision in the law punishing a person for violating any regulation made under the law. The appellant called attention to Section 4 of the Act to sustain its position. No stronger argument could be made in behalf of the appellee than reading Section 4 in so far as it refers to Section 3. Section 4 provides for the examination of specimens of foods and drugs and says who shall make such examination, not for the purpose of determining from such examination whether or not the regulation of the three several Secretaries has been violated, but to determine from such examination *whether such articles are adulterated or misbranded within the meaning of this Act.* "And if it shall appear from any such examination that any such specimen is adulterated or misbranded within the meaning of this Act, then the Secretary of Agriculture shall cause a notice thereof to be given to the party from whom such sample was obtained. Any party so notified shall be given an opportunity to be heard under such rules and regulations as may be prescribed as aforesaid [showing the regulations are merely administrative], *"and if it appear that any of the provisions of this Act have been violated by such party* (referring to violations under the Act, and not under the regulations), then the Secretary of Agriculture shall at once certify the facts to the proper United States District Attorney. * * * After judgment of the Court, notice shall be given by publication in such manner as may be prescribed *by the rules and regulations aforesaid.*"

In every part of Section 4 where the rules and regulations are referred to, they are shown to be rules and regulations for the administration of the law by the Department of Agriculture, and in the very same section it refers twice to an adulteration and misbranding *within the meaning of the Act.*

But, says the appellant, this is merely a matter of labelling and nothing more, and, therefore, being a matter of labelling, it is merely supplementary to and not an addition to the Act. Nowhere in the Act are the three Secretaries given power to prescribe the manner of labelling; but how can it be said that the requiring of an addition, stating something that a statute does not require, is merely prescribing a manner of labelling?

According to the United States Attorney this regulation could not be enforced in all cases, for he said in argument, as heretofore stated, that if the derivative does not follow in effect the parent, then persons could not be required under the regulation to state on their labels that such substance was a derivative of such parent.

We again refer to the fact that there is nothing in the law that would warrant the punishment of a person, or his goods, because he failed to label them as required by the three Secretaries; that the only punishment to be inflicted is a punishment for violating the law itself, and not any rule or regulation that the Department may adopt. But says the District Attorney, if we are not required to add thereto, after the word acetphenetidin, the word acetanilid, we are misleading and deceiving the public; that acetanilid is a well-known substance and acetphenetidin is not. Both, as we shall hereafter show, are denominated drugs in the United States Pharmacopœia of 1900. Both, as we shall hereafter show, are referred to in the United States Dispensatory, and there is not a medical dictionary or medical book on the subject of drugs that does not consider both of these drugs. Acetanilid has been criticized by the Government in certain bulletins issued by it, and acetanilid was at the hearings before the passage of the Pure Food Law considered an adulterant of acetphenetidin. This appears from the Government's own literature on this subject. And yet the Government representatives would now have us, in this case, add to the name of that which they say is a less harmful drug, and which they say in their literature is a drug of almost household use, an addition of the word "acetanilid," in order, as it were, to cast a cloud upon acetphenetidin. They claim to be acting on a high moral plane, when in fact, and in truth, if their contention is sustained, it will drive persons who manufacture these headache and other remedies to the use of the inferior drug, and thus give to the public that which the Government in its literature says is an adulterant of acetphenetidin. In fact, already certain large manufacturers have adopted, on account of this unlawful regulation, the use of acetanilid in the place of acetphenetidin. In fact, nearly all of the smaller manufacturers that make remedies of this character have, instead of coming into Court as we have done and contesting the right of the Government, merely resorted to the use of acetanilid, and the Government will by its action drive acetphenetidin from the market and compel persons to use acetanilid in lieu thereof, thus saving to the manufacturer and druggists hundreds of thousands of dollars.

The second point of the Government in answer to the argument and brief of the appellee, is that this libel should be sustained because it contains two paragraphs, and in the second paragraph thereof it says:

> "Your libelant further charges that each and all of said packages of drugs are further misbranded, in that the labels thereon are false and misleading, for the reason that each and all of said labels bear the statement that no acetanilid is contained therein, and that said statement imports and signifies that there is no quantity or proportion of any derivative of acetanilid contained in said drug."

In submitting this contention to the Court, the appellant concedes that the statement that there is no acetanilid in acetphenetidin is absolutely true; but claims that wherever drugs are labeled, "contains no acetanilid," it is thereby pretended that there is no quantity or proportion of acetphenetidin. The Government's attorney says that no man has a right to tell the truth. Appellant admits that the parent substance is not present when an article contains merely a derivative thereof, but insists that to say that the parent substance is absent is misleading and signifies the absence of the derivative. Such a proposition is so fallacious that to state it is to refute it. The appellant knowing that fact, however, says this is not an ordinary case; that acetanilid and its derivative acetphenetidin are kindred drugs; that they are chemically alike; that they are therapeutically alike; that their physiological effect is the same; and, therefore, to tell a person that there is no acetanilid therein is to tell him that acetphenetidin will not cure what acetanilid will cure; that acetphenetidin has none of the properties of acetanilid, and that acetphenetidin has none of the physiological effects of acetanilid. Just where the appellant obtained its knowledge of these propositions is unknown to appellee; and, if it were not for the fact that they devoted a large part of their additional brief to this subject, we would let the matter go unnoticed. There is no such issue here raised as is thus attempted to be raised by the appellant. The sole issue tendered by the libel on this branch of the case is whether or not the label is false and misleading when it says that there is no part of the parent substance contained in the drug, said statement being absolutely true; or, putting it another way, whether or not a statement which says that there is no part of the parent substance contained in the drug imports and signifies that there is no quantity or proportion of any derivative thereof.

A reading of the statement in the libel shows conclusively that the issue now attempted to be raised by the Government is not here in this case, and it is not here for two reasons: (1) it is not made an issue by the pleadings; and (2) the Court cannot take judicial notice of that which the appellant desires the Court on this hearing to notice judicially. If issue were joined on this libel, there would be no issue as to whether or not acetanilid and acetphenetidin are similar substances. There would be no issue that acetanilid and acetphenetidin have the same therapeutical effect, nor would there be any issue that acetanilid and acetphenetidin have the same physiological effect. All of these questions are beside the issue involved. At a trial, if issue were joined on this libel, the appellant would not be permitted to prove any of the contentions that it now raises. It could not show that there was acetanilid in acetphenetidin because this, it concedes, would be absolutely false. Nor could appellant put on the stand any chemist to show that these two substances were in any way chemically alike, nor could it call experts on therapeutics and physiology to show that they have the same therapeutical and physiological effect. The appellee would have no notice that such testimony was going to be offered because there is nothing in the libel attempting to raise any such issue. But, says the appellant, while all that may be true, yet this Court, on a hearing of the exceptions and objections, will take judicial notice of what is found in the encyclopedias and the dictionaries, and finding therefrom that these two substances are chemically similar, have the same therapeutical effect, and have the same physiological effect, will say (although the Court below was not asked to say, and although we were not given an opportunity to prove that such was not the fact) that all these things are true, and that, therefore, the true statement on the label that the article does not contain acetanilid is false and misleading. This is virtually an attempt to try *ex parte* the effect of these several drugs upon the human system, something that cannot be done, something that has never been done, and something that this Court will not do. If the appellant intended to raise any contentions like the ones now attempted to be raised we should have had some notice in the libel thereof. The libel merely says that when you say a parent substance is not in a certain drug, you import and imply that there is no derivative in the said drug. For instance, if you say, labelling a bottle of vaseline, "that it contains no kerosene," you mislead people, not because there is in vaseline no kerosene, but because vaseline is a derivative of kerosene; and when you say that there is no kerosene in vaseline, you import and signify that there is no derivative of kerosene therein. But let us answer this question of judicial notice. Appellant's counsel said on argument that the authorities cited in his brief sustain his contention as to judicial notice, and that the Court would take judicial notice of the chemical combination and the therapeutical and physiological effect of acetphenetidin and acetanilid, although all through the argument for appellant, both in the opening and closing, it was said that acetphenetidin was a drug comparatively unknown. On page 31 of the appellant's supplemental brief, it is said:

> "Acetphenetidin is intimately allied with acetanilid in its physiological action. This close relationship is recognized by all the standard medical dictionaries, and the Court will take judicial notice of the close relationship as a universally conceded scientific fact."

And appellant cites in support thereof *Luke vs. Calhoun,* 52 Ala., 115, in which case certain photographs of a deceased person were offered in evidence to identify the person who was killed. Objection was made thereto on the ground that there was no evidence that photography would produce a likeness. The Court, in admitting the photograph, it having been identified by some one as a photograph of the person deceased, said:

> "The courts will judicially notice the art of photography, the mechanical and chemical processes employed, the scientific principles on which they are based, and their results."

Another case cited is *Menominee River Sash Company vs. Milwaukee R. Company,* 91 Wis., 447. This was an action against a railroad company for damages by reason of sparks from an engine setting fire to the premises of the plaintiff. The Court said judicial notice may be taken of the fact that there is no device which will wholly prevent the escape of sparks and cinders from railway locomotives.

In another case cited, *Commonwealth vs. Pair,* 183 Mass., 242, where was involved the constitutionality of an act of the Legislature of Massachusetts, requiring compulsory vaccination, the Court said:

> "It is a fact of common knowledge that smallpox is a terrible disease, whose ravages have sometimes swept away thousands of human beings in a few weeks.

> It is equally well known that a large majority of the medical profession and of people generally consider vaccination, repeated at intervals of a few years, a preventive of the disease."

In this last-mentioned case, the defendant offered to prove what was vaccination and certain alleged injurious or dangerous effects of vaccination. This case was taken to the Supreme Court of the United States in the case of *Jacobson vs. Massachusetts,* 197 U. S., 23, and that Court, in considering whether or not this evidence was admissible, and referring to the facts that the defendant offered to prove and which the trial Court would not permit him to prove, said:

> "Each of them, in its nature, is such that it can not be stated as a truth, otherwise than as a matter of opinion. The only 'competent evidence' that could be presented to the Court to prove these propositions was the testimony of experts, giving their opinions. It would not have been competent to introduce the medical history of individual cases. Assuming that medical experts could have been found who would have testified in support of these propositions, and that it had become the duty of the judge, in accordance with the law as stated in *Commonwealth vs. Anthes,* 5 Gray, 185, to instruct the jury as to whether or not the statute is constitutional, he would have been obliged to consider the evidence in connection with facts of common knowledge, which the Court will always regard in passing upon the constitutionality of a statute. He would have considered this testimony of experts in connection with the facts that for nearly a century most of the members of the medical profession have regarded vaccination, repeated after intervals, as a preventive of smallpox; that while they have recognized the possibility of injury to an individual from carelessness in the performance of it, or even in a conceivable case without carelessness, they generally have considered

> the risk of such an injury too small to be seriously weighed as against the benefits coming from the discreet and proper use of the preventive; and that not only the medical profession and the people generally have for a long time entertained these opinions, but legislatures and courts have acted upon them with general unanimity. If the defendant had been permitted to introduce such expert testimony as he had in support of these several propositions, it could not have changed the result. It would not have justified the Court in holding that the legislature had transcended its power in enacting this statute on their judgment of what the welfare of the people demands. *Commonwealth vs. Jacobson,* 183 Mass., 242."

It will be seen here that the Supreme Court took notice of facts of common knowledge which the Court said will always be regarded in passing upon the constitutionality of a statute.

The contention that the Court would take judicial notice of the alleged intimate relation of acetphenetidin and acetanilid is not supported by the authorities cited by the appellant. The proper rule of judicial notice is as follows:

> "Courts will take judicial notice of the familiar and generally recognized principles of art and science. But the mere circumstance that facts are found in dictionaries, encyclopedias, or other books of reference will not warrant a Court in taking judicial notice of them unless they are of the requisite notoriety or are so connected with facts of such nature as to partake in a sense of this characteristic." 17 A. & E. Ency. of Law, 2d Ed., 909.

In support of this definition, we refer to the case of *Brown et al. vs. Piper,* 91 U. S., 37, where the Supreme Court of the United States took judicial notice of the artificial freezing of matter and held that a patent to preserve fish by freezing had no novelty.

Again in the case of *Eclipse Manufacturing Company vs. Adkins,* 36 Fed. Rep., 554, 556, the Court say:

> "But the Court must meet each case as it arises, and, in sustaining demurrers like this, keep strictly within the field of common knowledge. The practical difficulty and danger is in defining where special knowledge leaves off and common knowledge begins. The judge must always be careful to distinguish between his own special knowledge, and what he considers to be the knowledge of others in the field or sphere where the device in question is used. But, when the judge, before whom rights are claimed by virtue of a patent, can say from his own observation and experience that the patented device is in principle and mode of operation only an old and well-known device in common use, he may act upon such knowledge. The case must, however, be so plain as to leave no room for doubt, otherwise injustice may be done, and the right granted by the patent defeated, without a hearing upon the proofs. The judge must on all such questions vigilantly guard against acting upon expert or special knowledge of his own, instead of keeping strictly within the field of general or popular knowledge. While I do not intend to lay down a rule, I am free to say that I should not feel justified in holding a patent void for want for novelty on common knowledge, unless I could cite instances of common use, which would, at once, on the suggestion being made, strike persons of usual intelligence as a complete answer to the claim of such patent."

Also, in *Kaolatype Engraving Company vs. Hoke,* 30 Fed. Rep., 444, 446:

> "As the case has been presented, the question really before us is whether we will take judicial notice of certain processes described in various mechanical dictionaries, encyclopedias, and other publications produced on the hearing of the demurrer and, by reason

> of our taking judicial cognizance of such processes, determine that the patent in question does not describe an advance in the art to which it appertains, rising to the dignity of an invention. Besides those facts of which courts are bound by law to take judicial notice, they will ordinarily only take notice of facts of universal notoriety—of facts that are so generally understood that they may be regarded as forming part of the general knowledge of every person. *Brown vs. Piper,* 91 U. S., 41. The matters, of which we are asked to take judicial cognizance in this instance, and thereupon declare the invalidity of this patent, do not strike us as falling within the last category. They are a class of facts which might more properly be called to our attention on the hearing (with opportunity to the other side to rebut or explain) as tending to show the state of the art to which this patent appertains, and for the purpose of enabling us to determine whether this patent really describes a newly-discovered process which called for an exercise of the inventive faculty."

In the last case it will be noticed that the same contention is made as we make here: that this judicial notice is attempted to be invoked without opportunity on our side to rebut or explain the alleged facts desired by the appellant to be considered by the Court. From these authorities, it is submitted that this Court can not take judicial notice of the alleged facts that the appellant desires this Court in this case to judicially know. It might be said that if the appellant had tendered any issue to us on these questions, we would have met it, and met it by affirmatively showing that all of its contentions are absolutely erroneous. Indeed, the very Pure Food Law under which appellant is proceeding meets and denies its contention that acetanilid and acetphenetidin are kindred substances. This Court must take judicial notice of the United States Pharmacopœia, because Section 6 says:

> "That the term 'drug,' as used in this Act, shall include all medicines and preparations recognized in the United States Pharmacopœia or National Formulary for internal or external use, and any substance or mixture of substances intended to be used for the cure, mitigation, or prevention of disease of either man or other animals."

The Pharmacopœia defines both acetanilid and acetphenetidin. On page 3 acetanilid is defined as follows:

> "The monacetyl derivative [C_6H_5NH ($CH_3.CO$)] of aniline."

On Page 4 of the Pharmacopœia acetphenetidin is defined as follows:

> "A phenol derivative [Acetparaphenetidin, C_6H_4 (OC_2H_5) NH CH_3 CO_1:4], the product of the acetylization of para-amidophenetol."

The dose prescribed by the Pharmacopœia for acetanilid is 4 grains and the dose prescribed for acetphenetidin is 7½ grains.

As an appendix to this brief we give the printed matter of the Pharmacopœia on both acetanilid and acetphenetidin, the uses of both acetanilid and acetphenetidin as laid down in the United States Dispensatory and extracts from two Government documents, one Senate Report No. 301, and the other hearing on House Bill No. 3109, and request the Court to read them in connection with the contention of the appellant that these substances are chemically similar and alike in their therapeutical and physiological effects.

It appears from the definition in the Pharmacopœia that their chemical make-up is not alike; it appears from the documents annexed in the appendix that while the therapeutical effects are somewhat similar, the physiological effects are not the same. It appears from the Government documents that acetanilid is an adulterant of acetphenetidin, and as such is condemned not only by the published document containing the report of the Health Officer of the City of New York, but by Dr. Wiley himself. In fact, the Department of Agriculture itself has issued three bulletins, in which it makes comparisons between the drugs acetanilid and acetphenetidin, or as they call acetphenetidin, by its trade name "phenacetine," in all of which bulletins the Government attempts to show the greater safety of acetphenetidin.

The Bulletins are "Bureau of Chemistry Bulletin No. 126," "Farmers Bulletins Nos. 377 & 393." In Bulletin No. 126, the Department of Agriculture, after a thorough investigation reports the relative safety of acetanilid and phenacetine, as follows: To 911 cases of unfavorable results from the use of acetanilid, there are only 166 cases of unfavorable results from the use of phenacetine. To 144 cases of habitual use from acetanilid, there are 18 cases of habitual use from phenacetine.

The Department of Agriculture also found that phenacetine is regarded as the least dangerous of these drugs by 231 physicians, to 58 who considered acetanilid the least dangerous. In other words, 3 out of every 4 physicians consider phenacetine less dangerous than acetanilid, and therefore many of them prescribe Antikamnia because they know that it does not contain acetanilid, which they would not do if they had any doubt regarding this matter.

On page 33 of the supplemental brief the appellant says:

> "When purchasers read today on the label of a headache wafer or tablet the statement 'contains no acetanilid' they expect to receive a substance which contains no drug possessing the poisonous and habit-forming tendencies of acetanilid. The obvious intent of the statement is to create the belief that the properties of acetanilid are absent."

If the public do expect to receive what the brief says they expect to receive, there is no question but that a drug containing acetphenetidin or phenacetine, according to the bulletins of the Agricultural Department, is a drug that does not possess the poisonous and habit-forming tendencies of acetanilid, and is a drug, according to its chemical definition and according to the definition of the Agricultural Department, from which the properties of acetanilid are absent and, therefore, from the appellant's standpoint, the public receive what they expect to receive and the appellee has a right to put on his label "no acetanilid contained herein."

Again it might be said to be a well-known fact that in all of these headache remedies there was a substance similar to that of antipyrine; in other words, a coal tar product of some kind. Would not the appellee have a right to call attention to the fact that in its remedy was the higher grade substance, the higher price substance, the milder substance, acetphenetidin, and not the cheaper substance, the stronger substance, acetanilid? People who know the difference between the two drugs will not use acetanilid when they can use acetphenetidin. Therefore, when on the labels in this case, the statement appears that it contains no acetanilid, and does contain acetphenetidin, this tells such people that the drug they object to is not in the preparation, but the drug that they desire is there. Instead of being misleading, the label tells the people what they want to know. Of course, if we would have a supposititious habitual user, such as the Department in its circulars in relation to acetanilid refers to, this statement might mislead such person if he did not know acetphenetidin was a milder coal-tar product. However, our drugs are sold for the benefit of the public, and not for the supposititious habitual user of the Department of Agriculture.

The statement of the District Attorney to the Court that we were misleading the public by using the word acetphenetidin instead of the trade-name "phenacetine," is answered by saying that "phenacetine" is the trade-mark name of acetphenetidin, the trade-mark belonging to the Farbenfabriken of Elberfeld Company.

Dr. Wiley, in his hearing before the Senate Committee, so states, saying phenacetine, "the genuine article," is "protected by patent."

An examination of the labelling of different kinds of drugs will disclose the fact that where the acetphenetidin is purchased from the owner of the trade-mark, they use the word "phenacetine," thus a tablet is known as "Phenacetine and Quinine," manufactured by Sharp and Dohme, of Baltimore, Maryland, "Phenacetine and Salol Gelatine Coated Pills," produced by the same manufacturer. Again we have tablets "Phenacetine and Caffeine, No. 2," produced by the same manufacturer. On the other hand, a label on a product sold by E. R. Squibb and Sons, Brooklyn, New York, reads, "100 Tablets Salol and Acetphenetidin, Squibb," and on each of the packages mentioned the quantity of phenacetine and acetphenetidin is given.

On page 32 of the supplemental brief of the appellant it will appear that acetphenetidin is called "phenacetine" in the several definitions referred to on said page.

In conclusion, we desire to state that the appellee is a manufacturing chemist, making a large number of medicines, which medicines are prescribed by physicians and sold by druggists throughout the United States; that it has no desire to mislead or to deceive any one, and is perfectly willing that any one shall read on its remedies acetphenetidin wherever acetphenetidin is contained therein; that it has no desire to conceal anything, but it does desire to inform the public that it uses a drug that was well known at the time of the passage of the Pure Food Law; that it uses a drug that is milder than acetanilid, and in fact free therefrom. In the light of what the Department has said of acetanilid, it is not the desire of appellee when it puts into its remedies acetphenetidin to be compelled to write thereon "acetanilid."

Respectfully submitted,

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APPENDIX.

I.

The Pharmacopœia of the United States of America, speaking of Acetanilide, on page 3 says:

ACETANILIDUM.
Acetanilide.

C_8H_9NO—134.09,
The monacetyl derivative [C_6H_5NH (CH_3CO)] of aniline.

Colorless, shining, micaceous, crystalline laminæ, or a crystalline powder; odorless, having a slightly burning taste, and permanent in the air.

Soluble in 179 parts of water and in 2.5 parts of alcohol at 25° C. (77° F.); in 18 parts of boiling water, and in 0.4 part of boiling alcohol; also soluble in 12 parts of ether and 5 parts of chloroform at 25° C. (77° F.).

When heated to 113° C. (235.4° F.) Acetanilide melts, and at 295° C. (563° F.) it boils without decomposition.

Upon ignition it is consumed without leaving a weighable residue.

Solutions of Acetanilide is simple solvents are neutral to test-paper.

If 0.5 Gm. of Acetanilide be agitated with 5 Cc. of colorless sulphuric acid in a clean test-tube, it dissolves without imparting color to the liquid.

On heating O.1 Gm. of Acetanilide with 5 Cc. of concentrated solution of potassium hydroxide (1 in 4), the characteristic odor of aniline becomes noticeable. On now adding 1 Cc. of chloroform, and again heating, the disagreeable odor of phenyl isocyanide (a poisonous product) is evolved (distinction from methyl-acetanilide or antipyrine).

On boiling 0.1 Gm. of Acetanilide for several minutes with 2 Cc. of hydrochloric acid, a clear solution results, which, when mixed with 3 Cc. of an aqueous solution of phenol (1 in 20), and afterwards with 5 Cc. of a filtered, saturated solution of chlorinated lime, acquires a brownish-red color, becoming deep blue upon supersaturation with ammonia water.

On heating 0.1 Gm. of Acetanilide with 10 Cc. of water, filtering the solution when cold, and adding bromine T. S., drop by drop, to the filtrate, a whitish precipitate of parabromacetanilide is formed (distinction from antipyrine or acetphenetidin).

A cold saturated, aqueous solution of Acetanilide added to ferric chloride T. S., should not affect the color of the latter (absence of aniline salts and various allied substances).

Average Dose.—0.250 Gm.—250 milligrammes (4 Grains).

The Pharmacopœia of the United States of America, speaking of Acetphenetidin, on page 4 says:

ACETPHENETIDINUM.

Acetphenetidin.

$C_{10}H_{13}NO_2$—177.79.

A phenol derivative (acetparaphenetidin, C_6H_4 (OC_2H_5) $.NH_3.CO_1$:4), the product of the acetylization of para-amidophenetol.

White, glistening, crystalline scales or fine crystalline powder, odorless and tasteless.

It is soluble in 925 parts of water, 12 parts of alcohol, 63 parts of ether, and 20 parts of chloroform, at 25° C. (77° F.); in 70 parts of boiling water and in 2 parts of boiling alcohol.

Heated to between 134° and 135° C. (273.2 and 275° F.) it melts, and at a higher temperature burns without leaving a weighable residue.

It dissolves without color in sulphuric acid, but if shaken with nitric acid it is colored yellow, which color persists when heated.

If 0.1 Gm. of Acetphenetidin be boiled for one minute with 1 Cc. of concentrated hydrochloric acid and the solution diluted with 10 Cc. of water, cooled and filtered, it should yield on the addition of 3 drops of an aqueous solution of chromium trioxide (1 in 30) a ruby red color.

On heating 0.1 Gm. of Acetphenetidin with 5 Cc. of a concentrated solution of potassium hydroxide (1 in 4), the odor in aniline should not be perceptible.

If 0.1 Gm. of Acetphenetidin be boiled with 10 Cc. of water it should yield a solution which, when cooled and filtered, should not become turbid upon the addition of bromine T. S. in slight excess (absence of acetanilide).

If 0.1 Gm. of Acetphenetidin be boiled for one minute with 3 Cc. of solution of sodium hydroxide (1 in 2), the solution cooled, and then agitated with 5 Cc. of a solution of chlorinated soda, there should be produced a clear yellow liquid, and not a purplish-red or brownish-red cloudy liquid or precipitate (absence of acetanilide).

A mixture of 0.3 Gm. of Acetphenetidin with 1 Cc. of 90 per cent alcohol should not acquire a red tint when diluted with three times its volume of water and boiled with one drop of tenth-normal iodine V.s. (absence of paraphenetidin).

Average Dose.—0.500 Gm.—-500 miligrammes (7½ grains).

II.

The United States Dispensatory (page 8) gives the uses of acetanilid, as well as the effect:

"USES.—The effects of acetanilide upon man are very similar to those produced by antipyrine, namely, after small doses, quietness; after very large doses, malaise, a little headache, singing in the ears, weakness, and a peculiar cyanosis, with some tendency to somnolence, mydriasis, and, if there has been fever, marked fall of temperature usually accompanied by, but not dependent upon, a profuse sweat. After enormous doses complete coma and collapse have been noted. It has in rare instances caused collapse and cardiac failure, and a peculiar measles-like eruption is not very uncommon. Large toxic doses have caused in animals and in man anesthesia, loss of reflex activity, tremors, irregular failing respiration, convulsions, coma, and general paralysis. The cyanosis is due to the formation of methæmoglobin in the blood. In the animal system acetanilide appears to break up into acetic acid and aniline, the aniline in turn undergoing oxidation into paramidophenol, which unites with sulphuric acid to be eliminated as paramidophenol sulphate.

Death has, in a number of cases, been produced by acetanilide when used for medicinal purposes. Five grains (0.32 gm.) are alleged to have caused fatal heart failure (Ind Med. Jour., Sept., 1890); but there have been instances of recovery after the dose of an ounce (31 Gm.). Sixty grains (3.9 Gm.) have frequently been followed by serious collapse, and in some cases by death. It is also necessary to exercise some care in the external use of the drug, for various cases of severe poisoning have been reported as caused by such use.

There is a widespread but perhaps not well-grounded belief in the profession that accidents are more rare after acetanilide than after antipyrine, but the medicinal application of acetanilide seems to be identical with that of antipyrine, save only as it is modified by the insolubility of acetanilide. It is also somewhat more powerful than antipyrine, its full dose being ten grains (0.65 Gm.), repeated if necessary; preferably administered in capsules or wafers. For details of medicinal use, see *Antipyrina*. Acetanilide is germicidal, and seems to be especially active in inhibiting the growth of pathogenetic organisms. It is also analgesis, and affords a very useful dressing for wounds and ulcers. The drug itself may be used in the form of a fine powder, or an ointment may be employed in the strength of from 10 to 50 per cent. In certain mucous inflammations, as vaginitis and urethritis, a local application (20 to 40 grains to the fluid ounce) has been found very effective. Acetanalide may be given in the form of powder, suspended in mucilage of acacia and syrup, or in the form of tablets or capsules.

Dose, from five to eight grains (0.32 to 0.5 gm.)."

The United States Dispensatory (page 10) gives the uses of acetphenetidin, as well as the effect:

"USES.—Acetphenetidin was first introduced as an antipyretic by Hinsberg and Kast, who found that in order to produce toxic effects in the lower animals enormous doses are required. These cause vomiting, staggering, hurried respiration, somnolence, cyanosis, methæmoglobinization of the blood. In man no fatal cases of poisoning have been reported, but Hollopeter saw twenty-two and a half grains produce in a woman collapse, with cyanosis. Acetphenetidin would seem to be one of the safest, as it certainly is one of the most efficient drugs of its class. It is asserted that its antipyretic action is more gradual, more prolonged, and less apt to be attended with disagreeable symptoms than that of antipyrine and other allied drugs. The experiments of Ott and of Cerna and Carter appear to prove that the fall of temperature produced by acetphenetidin is due to a lessened production of animal heat caused by a direct influence of the drug upon the thermogenetic centres, and is not necessarily accompanied by any distinct alteration of the circulation. H. C. Wood, Jr. (Univ. Med. Mag., July, 1900), found that when it is given intravenously it has no effect on blood pressure, but that in enormous doses it paralyzes respiration. It seems also to be a depressant to the spinal cord. As an antipyretic and as an analgesic, acetphenetidin appears to cover in its usefulness the same range as does antipyrine. In nervous headaches the combination of it with caffeine (twelve grains to three) is often singularly advantageous. By many, acetphenetidin is believed to be less depressing than is antipyrine. Urticaria has been noted after its use, but it seems not to produce any characteristic eruption. According to Reuter, paraphenetidin, which is liable to occur in commercial phenacetin, is a dangerous poison, especially acting upon the kidneys.

Dose, from five to fifteen grains (0.32 to 1 Gm.)."

III.

58th Congress, 2d Session. | SENATE. | Report No. 301.

ADULTERATION OF FOODS, ETC.

January 15, 1904.—Ordered to be printed.

Mr. Heyburn, from the Committee on Manufactures, submitted the following:

REPORT.

(To accompany S. 198.)

The Committee on Manufactures, to whom was referred the bill (S. 198) for preventing the adulteration, misbranding, and imitation of foods, beverages, candies, drugs, and condiments in the District of Columbia and the Territories, and for regulating interstate traffic therein, and for other purposes, beg leave to report as follows:

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(Page 23.)

Senator McCumber. Speaking of these samples and the percentage of adulteration therein being much greater than it probably would be if all samples were examined, I notice, under date of January 14, 1903, in the New York *Evening Post,* an article in relation to sham phenacetin, in which it is stated that of 373 samples bought from as many retail druggists in the city of New York, 315 were found to be adulterated. Many of the samples consisted of acetanilid, which is a heart depressant and very cheap. It was found to be the most common substitute. This would indicate not only that the suspected article is adulterated, but that the entire supply is largely adulterated, as shown by the New York *Evening Post*, whose agents bought it generally and paid the high price for it. It is stated that the wholesale price of phenacetin is approximately $1 per ounce, while that of the adulterated article is about 25 cents a pound.

(Page 24.)

Doctor Wiley. That is a very peculiar case. Here is an article which is protected by patent right and is made in Germany. The patentees will not allow it to be made in this country, because by excluding it absolutely they get their own price for it. It is a trust article. Acetanilide, which is a very grave poison, has been substituted largely, because it has the same effect of curing headaches that phenacetin has; but it is very much more dangerous. Both are dangerous.

Senator McCumber. Phenacetin could be taken in very much larger quantities, if so prescribed.

Doctor Wiley. It is so much less injurious than acetanalide that there never should be any replacement. It is a fraud, a pure and simple adulteration. That would not be true of all drugs. Some kinds of drugs are very generally adulterated, while others are not adulterated at all, practically.

Perhaps the percentage might be different, but what I said in regard to the practice would be the same with respect to both. We found the same thing. We have examined that same subject in the Department of Agriculture in our drug laboratory, and we found adulterations of the same kind, but not to the same extent.

We find another adulteration, to which the makers of phenacetin are very much opposed, and that is what is called peddled phenacetin. In Canada phenacetin is worth about one-fourth as much as it is here, perhaps less than that. It is smuggled across the border—the genuine article—and sold largely in this country, contrary to law. That is a fraud on the makers, who are protected by patent.

IV.

EXTRACT FROM HEARING ON H. R. 3109, BEFORE THE COMMITTEE ON MANUFACTURES, UNITED STATES SENATE, BEING "AN ACT FOR PREVENTING THE ADULTERATION, MISBRANDING, AND IMITATION OF FOODS, BEVERAGES, CANDIES, DRUGS, AND CONDIMENTS IN THE DISTRICT OF COLUMBIA AND THE TERRITORIES, AND FOR REGULATING INTERSTATE TRAFFIC THEREIN, AND FOR OTHER PURPOSES."

Tuesday, January 20, 1903—10 a. m.

Hon. P. J. McCumber, Chairman.

The Chairman. What organizations are represented by those who are present this morning?

MR. CHARLES ROOME PARMELE introduced.

The Chairman. Please state your position; what official position, if any, do you occupy?

Mr. Parmele. I am a manufacturing chemist of New York City.

Mr. Chairman. What persons are here desiring hearings and what organization, if any, do they represent?

Mr. Parmele. Dr. Frank P. Foster, the author of Foster's Enclycopedic Medical Dictionary and editor New York Medical Journal; Prof. Smith Ely Jelliffe, professor in the College of Pharmacy, New York City, also editor of Medical News; Mr. William J. Evans, representing McKesson & Robbins, drug manufacturers and wholesale druggists; Edward G. Wells, representing the M. J. Breitenbach Company and the C. N. Crittenton Company; Edward M. Johnson, representing the American Ferment Company, and Samuel Owen, representing Cress and Owen Manufacturing Company. Shall I proceed, Mr. Chairman?

* * * * * * * * * * *

(Page 2):

Mr. Parmele. As an illustration, here is the Pharmacopœia and here is Dr. Foster's Encyclopedic Medical Dictionary—he considers this dictionary in some respects a back number—it is fairly comprehensive. Look at the two works (calling attention to the books—the Pharmacopœia, one volume, Dr. Foster's work in four volumes).

Only those who come in daily contact with this drug situation can appreciate the extent to which substitutions and adulterations exist, and if this definition as now in the bill should generally stand it would prevent action against the chief offenders, because the bulk of their dishonesty is in the handling of just those products which are now in the Pharmacopœia.

Take phenacetin, for instance. With your permission, Mr. Senator, I will read to you a report made by the president of the New York Board of Health, Dr. Ernest Lederle, to the sanitary superintendent of New York.

The Chairman. We will be glad to hear the report read.

Mr. Parmele (reads):

> (Department of Health, City of New York, southwest corner Fifty-fifth Street and Sixth Avenue, Borough of Manhattan, division of chemistry.)
>
> New York, January 10, 1903.
>
> To the Assistant Sanitary Superintendent.
>
> Sir: I respectfully present the following report on an examination made of samples of phenacetin powders dispensed by pharmacists in this city:
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> The adulteration and substitution of drugs is believed to be widespread and flagrant and is an evil which is a decided menace to life and health. In most cases such [page 3] adulteration or substitution can not readily be detected unless by chemical analysis. Not having the necessary expert chemical assistance at their command, both the physician and patient are placed at the mercy of the druggist, a situation which is understood and taken advantage of by the unscrupulous. The fact that the victims in these cases are already in bad health makes such action all the more pernicious; not only is the patient taking medicine which in many instances is doing direct injury, but the

physician is mystified by the strange action of drugs prescribed by him, when in reality his patient is taking something entirely different from the medicine called for by the prescription.

Careful inquiry elicited the information that one of the most commonly adulterated drugs and one for which cheaper substances are frequently substituted was phenacetin. This was consequently chosen as the first of a systematic investigation into the question of drug adulteration as a whole.

Phenacetin is an antipyretic so commonly used that it may practically be considered a household remedy, and is almost universally dispensed by druggists over the counter without a physician's prescription. The usual dose is from five to ten grains.

The wholesale price of phenacetin is approximately $1 per ounce, while that of its usual adulterant or substitute, acetanilid, is about 25 cents per pound. The financial inducement to substitute is consequently great.

As will be seen by the results obtained in this laboratory, however, acetanilid is not the only adulterant in use.

The samples examined were collected with the assistance of the division of inspections. In all, 373 samples were analyzed, collected in the boroughs of Manhattan and Brooklyn. Of these, 58 were pure phenacetin as labeled, 315 were adulterated or were cases of substitution.

Of the adulterated samples 267 were mixtures of phenacetin and acetanilid, 2 were mixtures of phenacetin and sugar, 4 were mixtures of phenacetin and starch, 32 were pure acetanilid, 4 were mixtures of acetanilid and cane sugar, 1 was a mixture of acetanilid and milk sugar, 3 were mixtures of acetanilid and starch, 1 was antipyrin, 1 was quinine sulphate.

Adulterated samples were purchased by inspectors of this department at the following pharmacies:

The names were not deemed necessary and therefore omitted.

> The prices paid by the inspectors for three 10-grain powders varied between 15 and 30 cents. A fair average would be 20 cents. If pure phenacetin is sold at this price, an ounce, costing $1, is sold for $3.20, a profit of over 200 per cent. Such a profit, however, does not appear to be sufficient. Acetanilid, costing about 2½ cents per ounce, is substituted and sold at the same price as pure phenacetin.
>
> No valid excuse can be made for this form of dishonesty. The claim can not even fairly be made that in some cases the druggist himself is the innocent victim of a fraud, for the reason generally given to justify the enormous percentage of profit charged by pharmacists is that the charge is made for the skill and special knowledge required in dispensing drugs and not for the intrinsic value of the drug sold. This appears to be a fair claim, but then, not to apply this special knowledge, while charging for it would be a fraud in itself. Moreover, ignorance and carelessness in dispensing drugs is, if anything, more dangerous to the public than deliberate dishonesty.

I want to enlarge upon one point; there were in all 373 samples of analyzed products—mark you, Mr. Chairman—53 were pure phenacetin as labeled, 315 were adulterated or were substitutions—nearly six times as many substitutions as originals.